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# Final clinical outcomes of nationwide precision oncology pilot study; KOrean Precision Medicine Networking Group Study of MOlecular profiling guided therapy based on genomic alterations in advanced Solid tumors (KOSMOS) KCSG AL-20-05

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## Background

- Next generation sequencing (NGS) has become widely available but molecular profiling guided therapy (MGT) had not been established in the real world due to a lack of available therapies and expertise to interpret and match treatment in Korea.

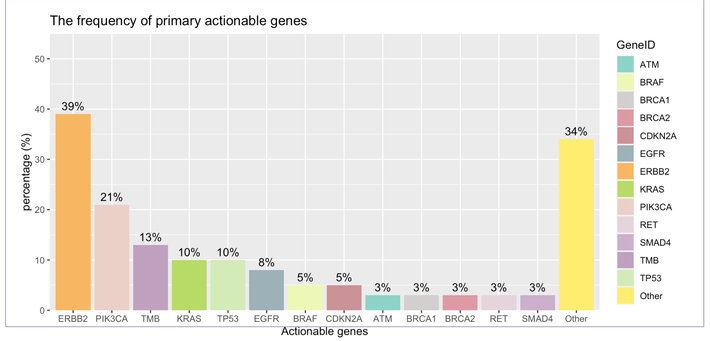
## Methods

- Patients with advanced or metastatic solid tumors with available NGS results and without standard treatment were enrolled. cMTB interpreted patients' NGS reports and recommended one of the three following options as previously described (https://doi.org/10.1016/j.esmoop.2022.100653);
- (1) the therapeutic use of investigational medicinal products (IMPs) (trastuzumab emtansine, trastuzumab and pertuzumab, atezolizumab, bevacizumab and erlotinib, alpelisib, capecitabine, dabrafenib and trametinib, alectinib, erlotinib and bevacizumab) outside of their approved indication based on genomic alterations, (2) alternative treatment options such as palliative care or radiotherapy, and (3) clinical trials.
- The primary variable was to assess the proportion of patients with actionable genomic alterations and patients receiving MGT as cMTB recommendations. The expected MGT matching rate was 30%. Other variables were treatment duration (TD), overall response rate (ORR), disease control rate (DCR), and safety.

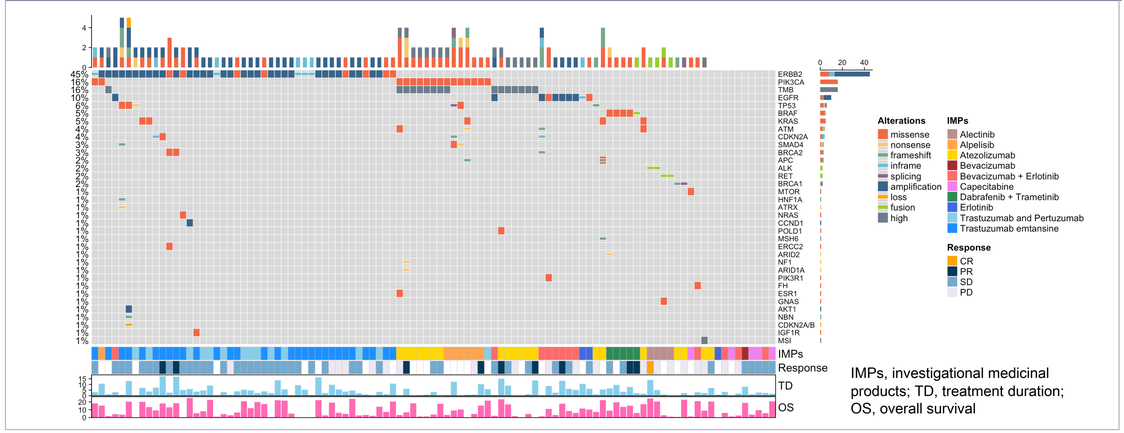
## Results

- From Feb 2021 to Feb 2022, 193 cases from 29 sites were discussed in 60 cMTB sessions. The median age was 58 (24-88) years, and 99 (51.0%) were men. Colorectal (22.3%), lung (15.0%), and breast cancer (11.9%) were the most common cancer types. The median line of previous treatments was 3 (0-12). The median time from case submission to the cMTB discussion and to treatment initiation with IMPs were 7 days (2-20) and 28 days (14-90), respectively.
- Actionable genetic alterations, including high tumor mutational burden (TMB) ≥ 10/Mb, and high MSI were found in 145 patients (75.1%). ERBB2 was the most commonly observed actionable gene (39%), followed by PIK3CA (21%), high TMB (13%), KRAS (10%), and EGFR (8%). (Figure 1)

### Figure 1. The frequency of primary actionable genes




### Figure 2. Primary genetic alterations in 101 patients who received IMPs

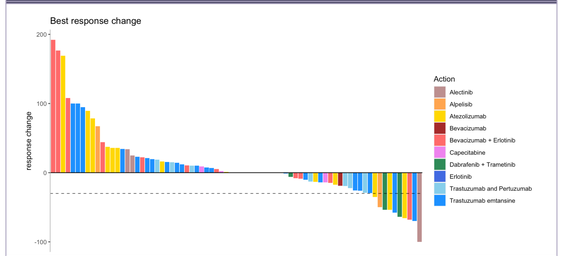



IMPs, investigational medicinal products; TD, treatment duration; OS, overall survival

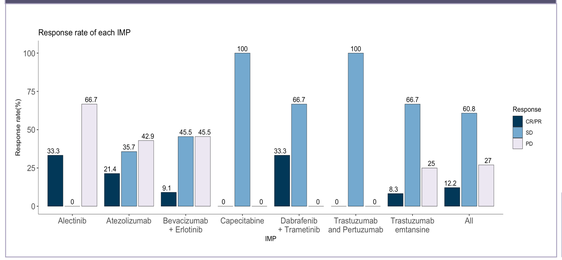
| IMPs | Total | Eval | CR | PR | SD | PD | ORR* | DCR* | 4M TD | TD | CI of TD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alectinib | 4 | 3 | 1 (33.3%) | 0 (0.0%) | 0 (0.0%) | 2 (66.7%) | 33.3% | 33.30% | 50% | 3.4 | 0.57-NA |
| Alpelisib | 7 | 2 | 0 (0.0%) | 1 (50.0%) | 0 (0.0%) | 1 (50.0%) | 50% | 50% | 42.9% | 1.4 | 0.97-NA |
| Atezolizumab | 20 | 14 | 0 (0.0%) | 3 (21.4%) | 5 (35.7%) | 6 (42.9%) | 21.4% | 57.10% | 30% | 1.9 | 0.7-6.5 |
| Bevacizumab | 1 | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) | 0% | 100% | 100% | 8.3 | NA-NA |
| Bevacizumab and Erlotinib | 12 | 11 | 0 (0.0%) | 1 (9.1%) | 5 (45.5%) | 5 (45.5%) | 9.1% | 54.5% | 33.3% | 3.4 | 2.8-NA |
| Capecitabine | 5 | 3 | 0 (0.0%) | 0 (0.0%) | 3 (100.0%) | 0 (0.0%) | 0% | 100% | 0% | 1.6 | 0.5-NA |
| Dabrafenib and Trametinib | 5 | 4 | 0 (0.0%) | 2 (50.0%) | 2 (50.0%) | 0 (0.0%) | 50% | 100% | 60% | 6.9 | 3.8-NA |
| Erlotinib | 3 | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) | 0% | 100% | 66.7% | 6.5 | 1.37-NA |
| Trastuzumab and Pertuzumab | 14 | 12 | 0 (0.0%) | 0 (0.0%) | 12 (100.0%) | 0 (0.0%) | 0% | 100% | 57.1% | 4.6 | 3.5-6.3 |
| Trastuzumab emtansine | 30 | 24 | 0 (0.0%) | 2 (8.3%) | 16 (66.7%) | 6 (25.0%) | 8.3% | 75% | 56.7% | 4.2 | 3.03-7.53 |
| All | 101 | 75 | 1 (1.3%) | 9 (12.0%) | 45 (60.0%) | 20 (26.7%) | 13.3% | 73.3% | 45.5% | 3.7 | 2.8-5.0 |

Eval, evaluable for tumor response; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; 4M TD, 4 months treatment duration; CI, confidential interval, *ORR and DCR were calculated only in patients who were available for tumor assessment.

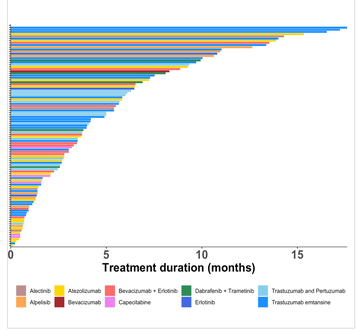
### Figure 3. Best response change from baseline




### Figure 4. Best response rate of each IMPs

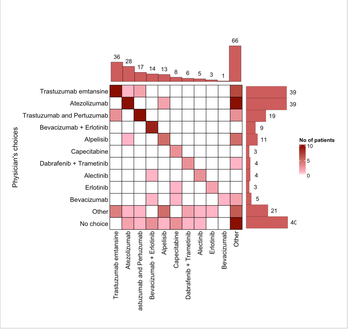



### Figure 5. Treatment duration




Among 101, 10 (9.9%) had TD ≥ 12 months, and 4 (4.0%) showed TD ≥ 15 months (Figure 5).

### Figure 6. Concordance rates between physicians' choice and MTB recommendations




The concordance rate between pre-MTB physicians' choice and MTB recommendations was 61.7% (119/193) (Figure 6).

## Adverse Events

| Adverse events | n | % |
|---|---|---|
| Diarrhea | 12 | 11.2 |
| Nausea | 11 | 10.3 |
| Decreased appetite | 10 | 9.3 |
| Vomiting | 8 | 7.5 |
| ALT/AST increased | 7 | 6.5 |
| Blood bilirubin increased | 7 | 6.5 |
| Pain | 7 | 6.5 |
| Pruritus | 7 | 6.5 |
| Thrombocytopenia | 6 | 5.6 |
| Anaemia | 5 | 4.7 |
| Asthenia | 5 | 4.7 |
| Pneumonia | 5 | 4.7 |
| Weight decreased | 5 | 4.7 |
| Constipation | 4 | 3.7 |
| Cough | 4 | 3.7 |

| Serious adverse events | n | % |
|---|---|---|
| Asthenia | 4 | 3.7 |
| Pneumonia | 4 | 3.7 |
| Blood bilirubin increased | 3 | 2.8 |
| Pain | 3 | 2.8 |
| Seizure | 2 | 1.9 |
| Vomiting | 2 | 1.9 |
| Abdominal distension | 1 | 0.9 |
| Abdominal pain | 1 | 0.9 |
| Back pain | 1 | 0.9 |
| Blood creatine increased | 1 | 0.9 |
| Cholecystitis acute | 1 | 0.9 |
| Closed fracture manipulation | 1 | 0.9 |
| Compression fracture | 1 | 0.9 |
| Depressed level of consciousness | 1 | 0.9 |
| Dyspepsia | 1 | 0.9 |

## Conclusions

- KOSMOS confirmed the feasibility of MGT by cMTB, achieving the pre-planned numbers of providing IMPs with a high matching rate of MGT (61.7%).
- KOSMOS also showed a modest ORR and a promising DCR and TD in heavily pre-treated patients, suggesting NGS-based MGT could be implemented in real practice if confirmed in a bigger sample size.
- Among 101 who received IMPs, 9.9% had long-term clinical benefit from MGT.
- KOSMOS-II (NCT05525858) is currently underway to confirm the significance of MGT in a larger number of patients (n≈1,000).

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